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(54) **BIOCOMPATIBLE AQUEOUS SOLUTION FOR USE IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS**

BIOKOMPATIBLE WÄSSRIGE LÖSUNG ZUR VERWENDUNG IN DER KONTINUIERLICHEN AMBULANTEN PERITONEALDIALYSE

SOLUTION AQUEUSE BIOCOMPATIBLE A USAGE EN DIALYSE PERITONEALE CONTINUE AMBULATOIRE

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EP 0 859 621 B1

Description

[0001] Continuous ambulatory peritoneal dialysis (CAPD) is used to treat end stage renal failure (ESRF) by introducing an osmotically active solution into the peritoneal cavity. Toxic waste products and excess fluid move from the blood into the diatysate solution by diffusion and ultrafiltration across the peritoneum. Osmotic ultrafiltration occurs as a result of the addition of hypertonic concentration of glucose to the dialysing solution, Due to the osmotic gradient between the blood and the CAPD solution the glucose draws water from the blood stream into the peritoneal cavity. The osmotic effect is transient and diminishes as the glucose is absorbed and/or metabolised.

[0002] In CAPD the dialysis solution is infused from collapsible plastic bags into the peritoneal cavity where it is retained for a period of time (referred to as the dwell time), after which it is drained and discarded. Generally, 3-5 treatments or exchanges of 1-3 litres each of CAPD solution are carried out daily, with an overnight dwell. The glucose concentration varies between 1.5 and 5% (w/v), with commercial CAPD solutions containing 1.5%, 2.5 or 4.5% glucose, with a high lactate content and various electrolytes which are present in more or less pH ysiologic concentrations. CAPD patients also lose 5-10 grams of protein into the dialysate per day. Commercial CAPD solutions typically have an osmolarity of 300-700 mOsm/L, preferably 350-450 mOsmol/L, as taught by US Patent 5,011,826.

[0003] Although peritoneal dialysis has some advantages over hemodialysis, including a substantial cost saving, there are several potential complications to CAPD. These include protein loss through the relatively highly permeable peritoneal membrane, absorption and metabolism of the added glucose resulting in weight gain and hyperlipidemia, which is particularly problematic in diabetic patients, who have a high incidence of ESRF (Ong- Ajyooth, L., Transp Proc 26: 2077, 1994).

[0004] An average patient absorbs about 150 grams of glucose from the dialysate per day, which for many patients is an excessive source of carbohydrate and results in hyperinsulinemia and hypertriglyceridemia in non-diabetic patients, which contributes to atherosclerotic disease. This series of events likely contributes to cardiovascular disease which is the most common cause of death among patients with ESRF.

[0005] Chronic exposure of the peritoneal membrane to the hypertonic and acidic CAPD solution (pH 5-6.2)can result in a loss of its function as an ultrafiltration membrane, leading to increased permeability of the peritoneal membrane and an increased rate of absorption of glucose from the dialysis solution and a loss of ultrafiltration capability. (Breborowicz et al Advances in Peritoneal Dialysis 8: 11, 1192 and Breborowicz et al Nephron 67: 350, 1994). Peritoneal biopsy samples from patients chronically dialysed with CAPD solutions show a typical epithelial reaction to irritation, mesothelial cell proliferation, as well as a decrease in the number of microvilli which normally line the mesothelial cell surface (Dobbie, J.W., Uoyd, J.K., Gall, C.A. In R. Khamma, K.D. et al Eds. Advances in peritoneal dialysis. Toronto. U of Toronto Press, 3, 1990: Friedlander, M. J Lab Clin Med 122: 639, 1993). A chronic inflammation of the peritoneum is also a consequence of chronic CAPD treatment, possibly related to the acidic nature of the CAPD solution (Lewis, S. & Holmes, C. Periton Dial Int 11: 14, 1991; Beelen, R.H.J. et al In Maher J.F., Winchester, J.F. Eds. Frontiers in peritoneal dialysis. New York: Field, Richj and Associates, 524, 1986; Bos, H.J. et at Nephron 59: 508, 1991), and which leads to healing (Weiczorowska, K. et al Perit. Dial. Int. 15:81, 1995. Morphologic changes in the peritoneal structure also occur with chronic CAPD therapy, including fibrosis of the peritoneum (Chaimovitz, C., Kidney Int 45: 1226, 1994). Further, the use of the current relatively acidic and glucose hypertonic CAPD solutions results in a decrease in the function of peritoneal macrophages, again indicating a need for more physiologic and biocompatible CAPD solutions (deFijter, C.W.H. et al Clin Nephrology 39: 75, 1993).

[0006] As well, it has been shown that there is a loss of glycosaminoglycans (GAG's) from the peritoneal membrane which results in a loss of filtration efficiency. It has been suggested that the loss of GAG's from the peritoneal membrane is a result of the increased production of free radicals by activated peritoneal leukocytes (Breborowicz, A. et al Periton Dial Int 11(Suppl): 35a, 1991) or because of a destructive action on interstitial tissue proteins (Fligiel, S.E.G. et al Amer J Pathol 115: 418, 1984). Supplementation of the dialysis fluid with the GAG chondroitin sulphate increases net ultrafiltration due to slower absorption of glucose and fluid from the peritoneal cavity (Advances in Peritoneal Dialysis 8: 11, 1992; Nephron 67: 346, 1994), possibly due to its ability to scavenge free radicals. Other GAG's, such as heparin and dermatan have also been reported to scavenge free radicals (Hiebert, L., Liu, J.M., Semin Thromb Hemost 17: 42, 1991; Fracasso, A. et al J Amer Soc Neph 5: 75p, 1994). It has also been reported that hyaluronan (formerly known as hyaluronic acid), which also scavenges free radicals, protects the peritoneum from injury resulting from CAPD treatment (Wieczorowska, K. et al Perit. Dial. Int. 15:81, 1995). Supporting this is the finding that the dialysis fluid collected overnight has a higher concentration of hyaluronan than serum. For example, Yung, S. et al (Kidney Int 46: 527, 1994) found that hyaluronan levels increased in the dialysate from ESRF patients with or without peritonitis undergoing CAPD treatment, and that the peritoneal mesothelial cells were the likely source of the hylauronan. Hyaluronan is important in the regulation of cell proliferation during healing. Hyaluronan is a polymer of repeating molecules of N-acetylglucosamine and glucuronic acid; dermatan is composed of repeating units of N-acetylglucosamine and iduronic acid, and chondroitin is made up of glucuronic acid and N-acetylgalactosamine.

[0007] Breborowicz and Oreopulos have submitted a PCT patent application (EP-555087-A1) (priority 92US-830721)

for the addition of free radical scavengers such as GAG's, including hyaluronic acid degradation products, to CAPD solutions during episodes of peritonitis to prevent against peritonitis-associated inflammatory reactions .

[0008] As noted above, N-acetylglucosamine (NAG) is a component of many GAG's. NAG is formed in almost all cells from glucose through a series of biochemical reactions which include the addition of the amine group from glutamine to glucose to form glucosamine, with N-acetylglucosamine being synthesized by way of acetyl-CoA, NAG then is converted to NAG-6-phosphate (which is converted into the epimer of NAG, N-acetyl-mannosamine 6-phosphate which is converted to N-acetylneuraminic acid 9-phosphate which is incorporated into sialic acids, gangliosides and glycoproteins), to NAG-1-phosphate (which is converted into UDP-N-acetylglucosamine (UDP-NAG) which is incorporated into GAG's such as chondroitins and glycoproteins). The UDP-NAG is also converted into GAG's such as hyaluronan and glycoproteins. Thus, NAG is the primary building block of many essential tissue components, whether they are comprised of NAG itself or related amino sugars such as N-acetylmannosamine and N-acetylgalactosamine.

[0009] It has been shown that orally administered glucosamine and N-acetylglucosamine (NAG) are absorbed and distributed throughout the body rapidly, and incorporated into tissues and presumably into the GAG's of the body. These compounds are incorporated into the GAG's of the peritoneal membrane to prevent their depletion thus maintaining the integrity of the peritoneal membrane, and preventing or at least slowing down, the loss of membrane function as an ultrafiltration membrane.

[0010] The present invention provides a peritoneal dialysis solution comprising an effective amount of at least one osmotically active agent selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein said at least one osmotically active agent is present as a monomer or an oligomer of 2 to 12 carbohydrate units.

[0011] According to a second aspect of the present invention, there is provided at least one compound for use as an osmotically active agent, selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein said at least one compound is present as a monomer or an oligomer of 2 to 12 carbohydrate units.

[0012] According to a third aspect of the present invention, there is provided either use of a peritoneal dialysis solution comprising at least one osmotically active agent selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein the osmotically active agent is present as a monomer or oligomer of 2-12 carbohydrate units; or

use of at least one compound selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein said compound is present as a monomer or an oligomer of 2-12 carbohydrate units;

in the manufacture of a medicament for performing peritoneal dialysis.

[0013] In a preferred embodiment, the above use is for reducing at least one complication associated with peritoneal dialysis such as: morphologic and functional deterioration of the peritoneal membrane; peritonitis; adverse metabolic consequences and related cardiovascular disease; protein malnutrition; and combinations thereof.

[0014] Thus, the replacement of part or all of the glucose in conventional CAPD solutions with amino sugars, especially NAG, provides a more biocompatible peritoneal dialysis solution, while providing the necessary osmotic effect required for the removal of excess water and also removal of waste substances by solvent drag from patients with ESRF undergoing CAPD treatment. Unlike glucose, which is utilized by almost all microorganisms as a source of energy, the amino sugars are relatively less metabolized and not as likely to support microbial growth thus reducing the tendency for patients undergoing chronic CAPD treatment to develop peritonitis, a common and serious adverse event associated with CAPD treatment. Because of the rapid removal of NAG and other amino sugars from the systemic circulation by way of their incorporation into GAG's and various amino sugar containing tissue components, the extent of metabolism into lipids is significantly reduced, thus reducing the risk of obesity, protein malnutrition, dyslipidemia and hypertriglyceridemia, hyperinsulinemia etc and the related adverse metabolic consequences.

[0015] In order for NAG and related amino sugars to be useful as osmotic agents in CAPD solutions they must have a high chemical purity similar to that which would be required for use in pharmaceutical products, which means a minimum purity of 98.5%. NAG which is of this purity can be manufactured by two methods. The first is the acid digestion of crude chitin, which is a linear polymer of repeating units of NAG obtained from crab and shrimp shells and other crustaceans, followed by isolation of the deacetylation of the individual NAG units to glucosamine. The glucosamine is isolated and crystallized to a high level of purity and then is reacetylated using acetic anhydride to N-acetylglucosamine, which is precipitated and recrystallized from alcohol, such that its purity is greater than 98.5%. The second method of manufacturing NAG, and the preferred method, is to obtain NAG from dried crustacean shell or crude chitin by direct enzymatic digestion with an ensemble of enzymes including chitinase and chitobiase, which degrades the chitin polymer of NAG into disaccharide units of chitobiose and then into monomer units of NAG directly, without having to undergo any organic synthetic step. The NAG is recrystallized from alcohol to a high degree of purity from ethanol. The enzymes required for this process are secreted into the growth media of various microorganisms, especially Serratia marcescens. Thus this method of manufacture not only provides NAG of a suitable purity for use in CAPD solutions

but also permits the relatively inexpensive production of NAG as the chitin or crustacean shells can be added directly to the cell-free growth medium from a culture of S. marcescens and the NAG readily isolated from the medium after a suitable reaction period. By varying the length of the enzymatic reaction time the production of polymers of varying units of NAG can be produced, which can be further refined and isolated as specific molecular weight entities by way of separation using available chromatographic techniques, and which can be isolated, crystallized and further purified by recrystallization using methods familiar to those skilled in the methods of carbohydrate chemistry isolation and purification.

[0016] US Patent 5, 011,826 teaches that CAPD solutions can use galactose alone or with glucose in varying ratios as the osmotically active agents, whereas US Patent 4,879,280 teaches that disaccharides such as lactose, saccharose, cellobiose etc can be used similarly, both together with suitable electrolyte additives. As well patent US 4,879,280 also shows the use of trisaccharides, oligosaccharides and polysaccharides of a molecular weight less than 400,000 such as raffinose, starch, inulin, pectin, dextrans, hydroxy-ethyl starch (HES) and the like. For example, colloidal polymers of glucose of 4-250 glucose units long and with an weight average molecular weight of about 16,200 and a number average molecular weight of 5,800 has been clinically evaluated as component of a CAPD solution (Kidney Int 46: 496, 1994: US Patent 4,886,789). The osmolality of a 7.5% solution of this glucose polymer, called Icodextrin, was 282 mOsm/kg and had a pH of 5.3. However, neither the available scientific literature nor the available patents teach the use of polymers or oligomers of amino sugars such as N-acetylglucosamine, N-acetylmannosamine or N-acetylgalactosamine and the like as the osmotically active components of CAPD solutions, which are the subject of the present invention.

[0017] Since the effectiveness of intraperitoneal dialysis depends on the presence of a hypertonic solution and osmolarity depends on the number of molecules in solution, large molecules such as GAG's provide little of value to the osmotic effect of the CAPD solution, and the dialysis solution must still contain excess glucose. Since N-acetylglucosamine and related amino sugars, as well as the other sugar and/or acidic carbohydrates making up the GAG's have molecular weights similar to that of glucose, they would be osmotically active. Therefore, the inclusion of amino sugars, particularly N-acetylglucosamine, in a CAPD solution at concentrations ranging from 0.5 to 5%, with or without the presence of glucose, will provide an effective dialysis solution while being more biocompatible with the peritoneal membrane and thus preventing or slowing down the morphologic and functional deterioration of the peritoneal membrane and extending the time over which ESRF patients may effectively use CAPD treatment. This provides several benefits, including substantial cost saving to the health care system by reducing the need for expensive hemodialysis, a lower rate of peritoneal infection for patients receiving CAPD treatment, a lesser risk of cardiovascular disease due to a reduction in the lipid changes typical of use of currently available CAPD solutions, and a better quality of life for such patients.

[0018] Currently marketed CAPD solutions have the following typical composition per 100 mL of solution. Dextrose anhydrous 1.5, 2.5 or 4.25 plus Sodium Chloride 567 mg, Sodium lactate 392 mg, Calcium Chloride dihydrate 23.9 mg and Magnesium Chloride hexahydrate 15.2 mg. On a milliequivalence basis this represents 132 mEq Na/L, 3.24 mEq Ca/L, 1.5 mEq Mg/L, 101.75 mEq CVL and 36 mEq lactate/L. Alternately, the solution may contain malate, acetate or succinate in place of lactate. The solution typically has an osmotic pressure of 347 mOsmol/L.

[0019] The CAPD solution of this invention is intended to provide similar electrolyte levels as currently available CAPD solutions, except that the osmotically active carbohydrate composition is different, being composed of acetylated and deacetylated amino sugars including N-acetylglucosamine, glucosamine, N-acetylgalactosamine, galactosamine, N-acetylmannosamine, mannosamine each alone, or in combination at varying concentrations or with varying concentrations of glucose, or oligomers of N-acetylglucosamine, N-acetylmannosamine, N-galactosamine, galactosamine, mannosamine, and glucosamine such that they are comprised of at least 2 carbohydrate units and not more than 12 units. The composition may be a mixture of oligomers of varying amounts of each oligomer either alone or in combination with each other. As well the CAPD solutions of this patent may contain additional osmotically active agents in varying proportions to the acetylated and deacetylated amino sugars such acidic carbohydrates which are also incorporated into the tissue glycosoaminoglycans (GAG's) such as glucuronic acid and iduronic acid.

[0020] In animal models of inflammatory bowel disease the colon becomes fribrotic, as does the peritoneum as a result of chronic intraperitoneal dialysis. The administration of a solution of NAG into the bowel of rats in which a chemically induced inflammatory bowel reaction with bowel wall thickening or fibrosis occurs, reduces in a dose dependent manner the fibrotic reaction to the inflammatory stimulus (Table 1). It is to be expected that in a similar manner NAG will prevent the development of fibrosis of the peritoneum in CAPD patients.

[0021] In addition to glucose CAPD solutions typically also contain a suitable number and quantity of electrolytes such that a more less physiologic solution is obtained. For example, lactate is included as a base substitute. Its absorption and metabolism will correct metabolic acidosis. Sodium is usually included at a concentration slightly lower to that found in plasma, or 132-137 mM/L, to promote sodium removal. Similarly, chloride is usually included in the CAPD solution at physiologic strengths of 100-110 mM/L.

[0022] The normal osmolarity of blood is approximately 280 mOsm/L, so that a CAPD solution must have a greater

osmotic value than this if it to be effective as a dialysis solution, and preferably it should have an osmotic pressure of 300-700 mOsm/L, and more specifically 310-560, or in a more limited range, of 350 to 450 mOsm/L (from US Patent 4,879,280).

Table 1

COLON FIBROSIS (AS MEASURED BY WEIGHT(gm) OF 8 cm OF COLON)	
INTRARECTAL ADMINISTRATION	**MEAN ± SEM**
Control (20 mg TNB* in 0.25 mL Ethanol)	2.301 ± 0.222
25 mg NAG/kg BWt 1 hr before TNB/EtOH	1.669 ± 0.142
50 mg NAG/kg BWt 1 hr before TNB/EtOH	1.339 ± 0.155
100 mg NAG/kg BWt 1 hr before TNB/EtOH	1.150 ± 0.068

* TNB = trinitrobenzenesulfonic acid

[0023] In experiments in which rats were dialyzed for 4 hours with Hanks Balances salt solution with either glucose or N-acetylglucosamine added at a concentration of 75 mM or 214 mM, at a pH of 7.35 - 7.4. The net utrafiltration was calculated as the difference between the drained volume of dialysate after 4 hours dwell time in the peritoneal cavity and the Infused volume (20 mL) of the dialysis fluid. As well, the concentration of urea and creatinine in the blood and the dialysis fluid were measured. Permeability of the peritoneal membrane to urea and creatinine, expressed as the Mass Transfer Area Coefficient which was calculated according to the method of Kredlet et al (Blood Purif 4: 194, 1986). The results, given in the Table below, clearly demonstrate that NAG results in a statistically significant increase In net ultrafiltration as well as peritoneal clearance of urea without increasing albumin or total protein loss into the dialysis fluid. In addition, the inclusion of NAG in the dialysate fluid stimulated the synthesis of hyaluronic acid, as shown by the more than 100% Increase in amount of hyaluronic acid secreted in the dialysis fluid compared to the glucose treated rats. These in vivo experiments clearly demonstrate that NAG is a more effective osmotic agent than glucose when used for peritoneal dialysis.

	Glucose 75 mM (N=11)	NAG 75 mM (N=14)	Glucose 214 mM (N=11)	NAG 214 mM (N=13)
Net Ultrofiltration (mL/4 hrs)	-0.44 ± 2.0	-0.11 ± 1.6	11.45 ± 1.2	14.45 ± 1.6*
Mass Transfer Area Coef for Urea (mL/ min)	0.344 ± 0.13	0.287 ± 0.13	0.212 ± 0.07	0.262 ± 0.15
Perltonoal Clearance of Ures (mL/min)	18.8 ± 2.2	18.4 ± 2.1	26.9 ± 2.0	30.0 ± 2.2**
Total Proteln Dalysate/Serum Ratio (%)	4.3 ± 1.0	4.4 ± 0.6	2.8 ± 0.4	3.1 ± 0.5
Albumin Dllaysate/ Serum Ratio (%)	4.0 ± 1.6	3.9 ± 1.2	1.6 ± 0.6	2.0 ± 0.9

* = statistically significant ('t'-test), $p < 0.001$

** = statistically significant ('test'-test), $p < 0.01$

(continued)

	Glucose 75 mM (N=11)	NAG 75 mM (N=14)	Glucose 214 mM (N=11)	NAG 214 mM (N=13)
in Hyaluronic Acid In Dlolyeate Fluid (ug/L)	103 ± 21	226 ± 93*	91 ± 31	217 ± 96***

*** = slatistically significant, P < 0.002

[0024] The stimulation of hyaluronic acid by N-acetylglucosamine was confirmed in tissue culture of human mesothelial cells.

[0025] The above experiments represent specific embodiments of the present invention, and thus no limitation of the present invention to these specific embodiments is intended.

Claims

1. A peritoneal dialysis solution comprising
an effective amount of at least one osmotically active agent selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein said at least one osmotically active agent is present as a monomer or an oligomer of 2 to 12 carbohydrate units.

2. The solution of Claim 1 wherein the acetylated amino sugar is selected from the group consisting of N-acetylglucosamine, N-acetylgalactosamine, and N-acetylmannosamine.

3. The solution of Claim 1 or 2 wherein the acetylated amino sugar is N-acetylglucosamine.

4. The solution of Claim 1 wherein the deacetylated amino sugar is selected from the group consisting of glucosamine, galactosamine and mannosamine.

5. The solution of any of Claims 1, 2, 3 or 4 wherein the solution further comprises at least one electrolyte selected from the group consisting of sodium, chloride, calcium, magnesium, lactate, malate, acetate, succinate and combinations thereof wherein said electrolyte is present as a pharmaceutically acceptable composition.

6. The solution of Claim 5 wherein:

   (a) the solution has a pharmaceutically acceptable pH and the pH is in the range of about 5.0 to 7.4;

   (b) sodium is present at a concentration in the range of 115 to 140 mEquiv/L;

   (c) calcium is present at a concentration in the range of 0.6 to 3.24 mEquiv/L;

   (d) chloride is present at a concentration in the range of 100 to 145 mEquiv/L;

   (e) magnesium is present at a concentration in the range of 0 to 2.0 mEquiv/L; and

   (f) lactate, malate, acetate or succinate is present at a concentration in the range of 30 to 45 mEquiv/L.

7. The solution of any of Claims 1, 2, 3, 4, 5 or 6 wherein the at least one osmotically active agent is present at a concentration of about 0.5 to 5.0% (w/v).

8. The solution of any of Claims 1, 2, 3, 4, 5, 6 or 7 wherein the solution further comprises at least one additional osmotically active agent selected from the group consisting of glucose, iduronic acid, glucuronic acid, and combinations thereof.

9. The solution of Claim 8 wherein the concentration of the at least one osmotically active agent, together with the at least one additional osmotically active agent is present at a concentration of between 0.5 to 5.0% (w/v).

10. At least one compound for use as an osmotically active agent, selected from the group consisting of an acetylated amino sugar, a deactylated amino sugar and combinations thereof, wherein said at least one compound is present as a monomer or an oligomer of 2 to 12 carbohydrate units.

11. At least one compound for use according to Claim 10, wherein the at least one compound is an acetylated amino sugar.

12. At least one compound for use according to Claim 10 or 11 wherein the acetylated amino sugar is selected from the group consisting of N-acetylglucosamine, N-acetylgalactosamine, and N-acetylmannosamine.

13. At least one compound for use according to any of Claims 10-12 wherein the acetylated amino sugar is N-acetylglucosamine.

14. At least one compound for use according to Claim 10 wherein the at least one compound is a deacetylated amino sugar.

15. At least one compound for use according to Claim 10 or 14 wherein the deacetylated amino sugar is selected from the group consisting of glucosamine, galactosamine, and mannosamine.

16. At least one compound for use according to any of Claims 10-15 wherein the at least one compound is in the form of a solution and further comprises an electrolyte selected from the group consisting of sodium, chloride, calcium, magnesium, lactate, malate, acetate, succinate and combinations thereof wherein said electrolyte is present as a pharmaceutically acceptable composition.

17. At least one compound for use according to Claim 16 wherein:

(a) the solution has a pharmaceutically acceptable pH and the pH is in the range of about 5.0 to 7.4;

(b) sodium is present at a concentration in the range of 115 to 140 mEquiv/L;

(c) calcium is present at a concentration in the range of 0.6 to 3.24 mEquiv/L;

(d) chloride is present at a concentration in the range of 100 to 145 mEquiv/L;

(e) magnesium is present at a concentration in the range of 0 to 2.0 mEquiv/L; and

(f) lactate, malate, acetate or succinate is present at a concentration in the range of 30 to 45 mEquiv/L.

18. At least one compound for use according to any of Claims 10-17 wherein the at least one compound is present in the form of a solution at a concentration of about 0.5 to 5.0% (w/v).

19. At least one compound for use according to any of Claims 10-18 wherein the at least one compound is in the form of a solution and further comprises at least one additional osmotically active agent selected from the group consisting of glucose, iduronic acid, glucuronic acid, and combinations thereof.

20. At least one compound for use according to Claim 19 wherein the concentration of the at least one compound together with the at least one additional osmotically active agent is present at a concentration of between 0.5 to 5.0% (w/v).

21. Use of a solution as claimed in any of Claims 1-9, or use of at least one compound selected from the group consisting of an acetylated amino sugar, a deacetylated amino sugar and combinations thereof, wherein said at least one compound is present as a monomer or an oligomer of 2 to 12 carbohydrate units, in the manufacture of a medicament for performing peritoneal dialysis.

22. The use as claimed in Claim 21 for treating renal failure.

23. The use as claimed in Claim 21 for reducing complications associated with peritoneal dialysis.

24. The use of Claim 23 for reducing the following complications:

(1) morphologic and functional deterioration of the peritoneal membrane;

(2) peritonitis;

(3) adverse metabolic consequences and related cardiovascular disease; and

(4) protein malnutrition.

Patentansprüche

1. Peritonealdialyselösung, umfassend
eine wirksame Menge mindestens eines osmotisch aktiven Mittels, ausgewählt aus der Gruppe, bestehend aus einem acetylierten Aminozucker, einem deacetylierten Aminozucker und Kombinationen derselben, worin dieses mindestens eine osmotisch aktive Mittel als Monomer oder Oligomer von 2 bis 12 Kohlenhydrateinheiten vorhanden ist.

2. Lösung gemäß Anspruch 1, worin der acetylierte Aminozucker ausgewählt ist aus der Gruppe, bestehend aus N-Acetylglucosamin, N-Acetylgalactosamin und N-Acetylmannosamin.

3. Die Lösung aus Anspruch 1 oder 2, worin der acetylierte Aminozucker N-Acetylglucosamin ist.

4. Die Lösung aus Anspruch 1, worin der deacetylierte Aminozucker ausgewählt ist aus der Gruppe, bestehend aus Glucosamin, Galactosamin und Mannosamin.

5. Lösung gemäß einem der Ansprüche 1, 2, 3 oder 4, worin die Lösung zusätzlich mindestens einen Elektrolyten umfasst, ausgewählt aus der Gruppe, bestehend aus Natrium, Chlorid, Calcium, Magnesium, Lactat, Malat, Acetat, Succinat und Kombinationen derselben, worin der Elektrolyt als pharmazeutisch annehmbare Zusammensetzung vorhanden ist.

6. Die Lösung aus Anspruch 5, worin:

(a) die Lösung einen pharmazeutisch annehmbaren pH-Wert aufweist und der pH-Wert im Bereich von etwa 5,0 bis 7,4 liegt;
(b) Natrium in einer Konzentration im Bereich von 115 bis 140 mÄquiv/L vorhanden ist;
(c) Calcium in einer Konzentration im Bereich von 0,6 bis 3,24 mÄquiv/L vorhanden ist;
(d) Chlorid in einer Konzentration im Bereich von 100 bis 145 mÄquiv/L vorhanden ist;
(e) Magnesium in einer Konzentration im Bereich von 0 bis 2,0 mÄquiv/L vorhanden ist; und
(f) Lactat, Malat, Acetat oder Succinat in einer Konzentration im Bereich von 30 bis 45 mÄquiv/L vorhanden sind.

7. Lösung gemäß einem der Ansprüche 1, 2, 3, 4, 5 oder 6, worin das mindestens eine osmotisch aktive Mittel in einer Konzentration von etwa 0,5 bis 5,0 % (Gewicht/Volumen) vorhanden ist.

8. Lösung gemäß einem der Ansprüche 1, 2, 3, 4, 5, 6 oder 7, worin die Lösung zusätzlich mindestens ein weiteres osmotisch aktives Mittel enthält, ausgewählt aus der Gruppe, bestehend aus Glucose, Iduronsäure, Glucoronsäure und Kombinationen derselben.

9. Lösung gemäß Anspruch 8, worin die Konzentration des mindestens einen osmotisch aktiv Mittels, zusammen mit dem mindestens einen weiteren osmotisch aktiven Mittel in einer Konzentration von zwischen 0,5 bis 5,0 % (Gewicht/Volumen) vorhanden ist.

10. Mindestens eine Verbindung für die Verwendung als ein osmotisch aktives Mittel, ausgewählt aus der Gruppe, bestehend aus einem acetylierten Aminozucker, einem deacetylierten Aminozucker und Kombinationen derselben, worin die mindestens eine Verbindung als Monomer oder als ein Oligomer von 2 bis 12 Kohlenhydrateinheiten

vorhanden ist.

11. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 10, worin die mindestens eine Verbindung ein acetylierter Aminozucker ist.

12. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 10 oder 11, worin der acetylierte Aminozucker ausgewählt ist aus der Gruppe, bestehend aus N-Acetylglucosamin, N-Acetylgalactosamin und N-Acetylmannosamin.

13. Mindestens eine Verbindung für die Verwendung gemäß einem der Ansprüche 10 bis 12, worin der acetylierte Aminozucker N-Acetylglucosamin ist.

14. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 10, worin die mindestens eine Verbindung ein deacetylierter Aminozucker ist.

15. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 10 oder 14, worin der deacetylierte Aminozukker ausgewählt ist aus der Gruppe, bestehend aus Glucosamin, Galactosamin und Mannosamin.

16. Mindestens eine Verbindung für die Verwendung gemäß einem der Ansprüche 10 bis 15, worin die mindestens eine Verbindung in Form einer Lösung vorliegt und zusätzlich einen Elektrolyten umfasst, ausgewählt aus der Gruppe, bestehend aus Natrium, Chlorid, Calcium, Magnesium, Lactat, Malat, Acetat, Succinat und Kombinationen derselben, worin der Elektrolyt als eine pharmazeutisch annehmbare Zusammensetzung vorhanden ist.

17. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 16, worin:

(a) die Lösung einen pharmazeutisch annehmbaren pH-Wert aufweist und der pH-Wert im Bereich von etwa 5,0 bis 7,4 liegt;
(b) Natrium in einer Konzentration im Bereich von 115 bis 140 mÄquiv/L vorhanden ist;
(c) Calcium in einer Konzentration im Bereich von 0,6 bis 3,24 mÄquiv/L vorhanden ist;
(d) Chlorid in einer Konzentration im Bereich von 100 bis 145 mÄquiv/L vorhanden ist;
(e) Magnesium in einer Konzentration im Bereich von 0 bis 2,0 mÄquiv/L vorhanden ist; und
(f) Lactat, Malat, Acetat oder Succinat in einer Konzentration im Bereich von 30 bis 45 mÄquiv/L vorhanden sind.

18. Mindestens eine Verbindung für die Verwendung gemäß einem der Ansprüche 10 bis 17, worin die mindestens eine Verbindung in Form einer Lösung mit einer Konzentration von etwa 0,5 bis 5,0 % (Gewicht/Volumen) vorhanden ist.

19. Mindestens eine Verbindung für die Verwendung gemäß einem der Ansprüche 10 bis 18, worin die mindestens eine Verbindung in Form einer Lösung vorliegt und zusätzlich mindestens ein weiteres osmotisch aktives Mittel umfasst, ausgewählt aus der Gruppe, bestehend aus Glucose, Iduronsäure, Glucoronsäure und Kombinationen derselben.

20. Mindestens eine Verbindung für die Verwendung gemäß Anspruch 19, worin die Konzentration der mindestens einen Verbindung zusammen mit dem mindestens einen weiteren osmotisch aktiven Mittel in einer Konzentration von zwischen 0,5 bis 5,0 % (Gewicht/Volumen) vorliegt.

21. Verwendung einer Lösung, wie in einem der Ansprüche 1-9 beansprucht, oder Verwendung mindestens einer Verbindung, ausgewählt aus der Gruppe, bestehend aus einem acetylierten Aminozucker, einem deacetylierten Aminozucker und Kombinationen derselben, worin die mindestens eine Verbindung als ein Monomer oder ein Oligomer von 2 bis 12 Kohlenhydrateinheiten vorliegt, bei der Herstellung eines Medikaments zur Durchführung der Peritonealdialyse.

22. Die Verwendung gemäß Anspruch 21 zur Behandlung des Nierenversagens.

23. Die Verwendung gemäß Anspruch 21 zum Verringern von mit der Peritonealdialyse verbundenen Komplikationen.

24. Verwendung gemäß Anspruch 23 zum Verringern der folgenden Komplikationen:

(1) morphologische und funktionale Verschlechterung der Peritonealmembran;
(2) der Peritonitis (Bauchfellentzündung);
(3) widriger metabolischer Folgen und damit verbundener kardiovaskulärer Erkrankungen; und
(4) Proteinfehlernährungen.

Revendications

1. Solution de dialyse péritonéale comprenant une quantité efficace d'au moins un agent à activité osmotique choisi dans le groupe constitué par un aminosucre acétylé, un aminosucre désacétylé et leurs combinaisons, ledit agent à activité osmotique étant présent sous forme d'un monomère ou d'un oligomère de 2 à 12 unités d'hydrate de carbone.

2. Solution selon la revendication 1, dans laquelle l'aminosucre acétylé est choisi dans le groupe constitué par la N-acétylglucosamine, la N-acétylgalactosamine et la N-acétylmannosamine.

3. Solution selon la revendication 1 ou 2, dans laquelle l'aminosucre acétylé est la N-acétylglucosamine.

4. Solution selon la revendication 1, dans laquelle l'aminosucre désacétylé est choisi dans le groupe constitué par la glucosamine, la galactosamine et la mannosamine.

5. Solution selon l'une quelconque des revendications 1, 2, 3 ou 4, dans laquelle la solution comprend en outre au moins un électrolyte choisi dans le groupe constitué par le sodium, le chlorure, le calcium, le magnésium, le lactate, le malate, l'acétate, le succinate et leurs combinaisons, ledit électrolyte étant présent sous forme d'une composition pharmaceutiquement acceptable.

6. Solution selon la revendication 5, dans laquelle:

   (a) la solution a un pH pharmaceutiquement acceptable et le pH est compris entre environ 5,0 et 7,4;
   (b) du sodium est présent à une concentration comprise entre 115 et 140 méq/l;
   (c) du calcium est présent à une concentration comprise entre 0,6 et 3,24 méq/l;
   (d) du chlorure est présent à une concentration comprise entre 100 et 145 méq/l;
   (e) du magnésium est présent à une concentration comprise entre 0 et 2,0 méq/l; et
   (f) du lactate, du malate, de l'acétate ou du succinate est présent à une concentration comprise entre 30 et 45 méq/l.

7. Solution selon l'une quelconque des revendications 1, 2, 3, 4, 5 ou 6, dans laquelle au moins un agent à activité osmotique est présent à une concentration d'environ 0,5 à 5,0 % (masse/volume).

8. Solution selon l'une quelconque des revendications 1, 2, 3, 4, 5, 6 ou 7, la solution comprenant en outre au moins un autre agent à activité osmotique choisi dans le groupe constitué par le glucose, l'acide iduronique, l'acide glucuronique et leurs combinaisons.

9. Solution selon la revendication 8, dans laquelle la concentration dudit agent à activité osmotique avec ledit autre agent à activité osmotique est comprise entre 0,5 et 5,0 % (masse/volume).

10. Composé destiné à une utilisation comme agent à activité osmotique, choisi dans le groupe constitué par un aminosucre acétylé, un aminosucre désacétylé et leurs combinaisons, ledit composé étant présent sous forme de monomère ou d'un oligomère de 2 à 12 unités d'hydrate de carbone.

11. Composé destiné à une utilisation selon la revendication 10 dans laquelle ledit composé est un aminosucre acétylé.

12. Composé destiné à une utilisation selon la revendication 10 ou 11 dans laquelle l'aminosucre acétylé est choisi dans le groupe constitué par la N-acétylglucosamine, la N-acétylgalactosamine et la N-acétylmannosamine.

13. Composé destiné à une utilisation selon l'une quelconque des revendications 10 à 12 dans laquelle l'aminosucre acétylé est la N-acétylglucosamine.

14. Composé destiné à une utilisation selon la revendication 10 dans laquelle le composé est un aminosucre désacétylé.

15. Composé destiné à une utilisation selon la revendication 10 ou 14 dans laquelle l'aminosucre désacétylé est choisi dans le groupe constitué par la glucosamine, la galactosamine et la mannosamine.

16. Composé destiné à une utilisation selon l'une quelconque des revendications 10 à 15 dans laquelle le composé est sous forme d'une solution et comprend en outre un électrolyte choisi dans le groupe constitué par le sodium, le chlorure, le calcium, le magnésium, le lactate, le malate, l'acétate, le succinate et leurs combinaisons, ledit électrolyte étant présent sous forme d'une composition pharmaceutiquement acceptable.

17. Composé destiné à une utilisation selon la revendication 16 dans laquelle

(a) la solution a un pH pharmaceutiquement acceptable et le pH est compris entre environ 5,0 et 7,4;
(b) du sodium est présent à une concentration comprise entre 115 et 140 méq/l;
(c) du calcium est présent à une concentration comprise entre 0,6 et 3,24 méq/l;
(d) du chlorure est présent à une concentration comprise entre 100 et 145 méq/l;
(e) du magnésium est présent à une concentration comprise entre 0 et 2,0 méq/l;
et
(f) du lactate, du malate, de l'acétate ou du succinate est présent à une concentration comprise entre 30 et 45 méq/l.

18. Composé destiné à une utilisation selon l'une quelconque des revendications 10 à 17 dans laquelle ce composé est présent à une concentration d'environ 0,5 à 5,0 % (masse/volume).

19. Composé destiné à une utilisation selon l'une quelconque des revendications 10 à 18 dans laquelle le composé est sous forme d'une solution et comprend en outre au moins un autre agent à activité osmotique choisi dans le groupe constitué par le glucose, l'acide iduronique, l'acide glucuronique et leurs combinaisons.

20. Composé destiné à une utilisation selon la revendication 19 dans laquelle la concentration dudit composé avec l'autre agent à activité osmotique est comprise entre 0,5 et 5,0 % (masse/volume).

21. Utilisation d'une solution selon l'une quelconque des revendications 1 à 9, ou utilisation d'au moins un composé choisi dans le groupe constitué par un aminosucre acétylé, un aminosucre désacétylé et leurs combinaisons, ledit composé étant présent sous forme de monomère ou d'un oligomère de 2 à 12 unités d'hydrate de carbone, dans la préparation d'un médicament pour la mise en oeuvre d'une dialyse péritonéale.

22. Utilisation selon la revendication 21 pour le traitement de l'insuffisance rénale.

23. Utilisation selon la revendication 21 pour la réduction des complications associées à la dialyse péritonéale.

24. Utilisation selon la revendication 23 pour la réduction des complications suivantes:

(1) la détérioration morphologique et fonctionnelle de la membrane péritonéale;
(2) la péritonite;
(3) les conséquences métaboliques défavorables et les maladies cardiovasculaires apparentées; et
(4) la malnutrition protéique.